studies made from autopsies have been confirmed. In addition it has been shown that in occasional animals exoerythrocytic stages were encountered which spontaneously disappeared, although this finding is infrequent. From the standpoint of chemotherapy, it has been found that sulfadiazine will prevent the appearance of these forms. Likewise this same drug or sulfapyrazine will effect a cure and cause a disappearance of exoerythrocytic schizonts even after they have made their appearance. Quinine and atebrin have no prophylactic or curative action. Plasmochin has a questionable therapeutic effect. The implications of this study are evident if it is eventually shown that exoerythrocytic schizogony is an integral part of human malarial infections. However, regardless of its place in the life cycle of plasmodial infections, the fact that these forms respond so readily to some of the sulfonamide compounds and yet are totally refractory to quinine or atebrin furnish another lead in the study of malarial chemotherapy.

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Some Chemotherapeutic Properties of Sulfaquinoxaline.

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Following the synthesis of sulfaquinoxaline by Weijlard, Erickson, and Tishler[1] and the report by Seeler *et al.*[2] on the pharmacological properties of this compound, it was thought of interest to determine the *in vitro* and *in vivo* efficacy of this drug against certain bacteria.

In Vitro. Using a modification of Kolmer's method[3] and a strain of *E. coli* grown in a synthetic medium,[4] sulfaquinoxaline was found to be 4 times as effective as sulfanilamide and 32 times less effective than sulfadiazine. As reported for other sulfonamides, sulfaquinoxaline was mainly bacteriostatic and not bactericidal. Thus over a 72-hour incubation period, sulfaquinoxaline, sulfanilamide, and sulfadiazine caused complete inhibition of the test organism in dilutions of 1:64,000, 1:16,000, and 1:2,000,000 respectively. As previously observed with the sulfonamides,[5] sulfaquinoxaline caused definite morphological changes in dilutions far greater than those required to inhibit the growth of the organism.

In Vivo. For the *in vivo* tests, mouse-virulent strains of *Diplococcus pneumoniæ* Type I, *Streptococcus hemolyticus* 1685, *Salmonella schottmülleri,* and *Salmonella aertrycke* were used. Details of maintaining the growth and virulence of these cultures have been described in a previous paper.[6]

The mice were infected by intraperitoneal injections of 0.5 cc of 10^{-4} to 10^{-6} dilutions of a six-hour culture of the above organisms. The amounts of culture were adjusted to equal approximately 10,000-100,000 lethal doses, as determined by titration in mice. All experiments were performed using suspensions of sulfaquinoxaline, sulfadiazine, and sulfathiazole prepared immediately before use by grinding the powder in 10% gum acacia. Treatment with the 3 drugs was given by oral administration immediately following the bacterial inoculation. Subsequent therapy with sulfaquinoxaline was given once every 24 hours, together with 0.5 mg/mouse of vitamin K_1. It has been shown by Seeler *et al.*[2] that sulfaquinoxaline produces a hypoprothrombinemia which can be prevented by feeding

[1] Weijlard, J., Erickson, A. E., and Tishler, M., in press.

[2] Seeler, A. O., *et al.*, in press.

[3] Kolmer, J. A., and Boerner, F., *Approved Laboratory Technic,* 3rd Ed., 1941.

[4] Kohn, H. I., and Harris, Jerome S., *J. Pharm. and Exp. Ther.,* 1941, **73**, 344.

[5] Lockwood, J., *J. Immunol.,* 1938, **35**, 155.

[6] Robinson, H. J., *J. Pharm. and Exp. Ther.,* 1943, **17**, 70.

TABLE I.

Efficacy of Sulfaquinoxaline in Mice Infected with *D. pneumoniæ*. (Oral Therapy.)

Organism: *Diplococcus pneumoniæ* Type I, No. 37.
Age of Culture: 6 hours.
Infection: 0.5 cc of a 10^{-6} dilution in broth.
Therapy: Sulfaquinoxaline, sulfadiazine, or sulfathiazole given immediately after bacterial inoculation.

No. of mice	Drug	Mg/dose	No. of doses/day	Culture dilution	No. surviving in days 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	% Survival
				Therapy: Single daily doses over a 5-day period.																
40	Sulfaquinoxaline*	5	1	10^{-6}	39	30	25	17	12	8	7	5	5	5	5	5	4	4	4	10
80		10	1	"	79	72	60	49	44	35	28	23	19	19	19	19	17	17	17	21.3
80		20	1	"	80	79	75	69	66	54	48	40	39	38	37	37	37	36	36	45
40		40	1	"	40	39	36	35	35	34	29	29	29	29	29	29	29	29	29	72.5
40	Sulfadiazine	5	1	10^{-6}	38	23	12	5	5	4	2	2	2	2	2	2	2	2	2	5
80		10	1	"	79	49	29	25	19	14	8	7	4	4	4	3	3	3	3	3.8
80		20	1	"	80	69	65	41	33	30	28	20	18	18	17	17	17	17	17	21.3
40		40	1	"	39	39	38	28	23	21	19	17	15	15	13	13	12	11	11	27.5
40	Sulfathiazole	10	1	10^{-6}	24	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40		20	1	"	31	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
				Therapy: Every 6 hrs over a 5-day period.																
10	Sulfaquinoxaline*	1.25	4	10^{-6}	7	5	4	2	1	1	1	0	0	0	0	0	0	0	0	0
10		2.5	4	"	9	8	7	3	2	2	2	2	2	2	2	2	2	2	2	20
10		5.0	4	"	9	6	6	4	3	3	3	3	3	3	3	3	3	3	3	30
10	Sulfadiazine	1.25	4	10^{-6}	8	5	4	3	1	1	0	0	0	0	0	0	0	0	0	0
30		2.5	4	"	30	29	25	23	20	20	10	8	8	8	8	7	7	7	7	23.3
30		5.0	4	"	30	30	30	25	23	22	21	16	15	15	15	15	15	15	15	50
20	Sulfathiazole	2.5	4	10^{-6}	20	13	5	5	3	1	0	0	0	0	0	0	0	0	0	0
20		5.0	4	"	19	18	15	13	9	3	2	0	0	0	0	0	0	0	0	0
				Therapy: 0.																
90	Controls*	—	—	10^{-6}	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50		—	—	10^{-7}	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50		—	—	10^{-8}	17	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
50		—	—	10^{-9}	31	6	1	1	1	1	1	1	1	1	1	1	1	1	1	2

* Mice also received 0.5 mg vitamin K_1 daily by oral administration.

TABLE II.

Efficacy of Sulfaquinoxaline in Mice Infected with *S. schottmülleri* (Oral Therapy).

Organism: *Salmonella schottmülleri.*
Age of Culture: 6 hours.
Infection: 0.5 cc of a 10–5 culture dilution in 4% mucin.
Therapy: Sulfaquinoxaline, sulfadiazine, or sulfathiazole given immediately after bacterial inoculation.
No. of Mice: 20 to each level.

Drug	Mg/dose	No. of doses/day	Culture dilution	No. surviving in days															% Survival
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Therapy: Single daily doses over a 5-day period.																			
Sulfaquinoxaline*	5	1	10–5	18	17	13	11	10	10	10	10	10	10	10	10	10	10	10	50
	10	1	”	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	100
	20	1	”	20	20	19	18	18	18	18	18	18	18	18	18	18	17	17	85
Sulfadiazine	5	1	10–5	18	18	18	18	17	17	17	17	17	17	17	17	17	17	17	85
	10	1	”	17	16	14	14	14	13	12	12	10	10	10	10	10	10	10	50
	20	1	”	19	19	18	18	18	18	18	18	15	14	12	12	12	12	12	60
Therapy: Every 6 hrs over a 5-day period.																			
”	2.5	4	10–5	20	20	20	19	19	19	19	18	18	18	18	18	18	18	18	90
	5.0	4	”	20	20	19	19	17	14	12	10	10	10	10	10	10	10	10	50
Sulfathiazole	2.5	4	10–5	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	100
	5.0	4	”	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	100
Controls*	—	—	10–5	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
	—	—	10–6	9	2	2	2	2	2	1	1	1	1	0	0	0	0	0	0
	—	—	10–7	13	9	9	9	9	8	7	7	7	7	7	7	7	7	7	35
	—	—	10–8	15	10	9	9	9	9	9	9	9	8	8	8	8	8	8	40

* Mice also received 0.5 mg vitamin K_1 once daily by oral administration.

vitamin K1. For comparison, sulfadiazine and sulfathiazole were given once every 24 hours to one group of mice and every 6 hours to another group. The results of these experiments are given in Tables I and II. For simplicity, only the results at daily intervals with *D. pneumoniæ* and *S. schottmülleri* are given. Essentially the same findings were obtained with *Strep. hemolyticus* and *S. aertrycke*.

When all 3 drugs were given once daily, sulfaquinoxaline was superior to sulfadiazine or sulfathiazole, in that a single daily dose of 40 mg per mouse protected 72.5% of the mice infected with *D. pneumoniæ* Type I. Under the same conditions sulfadiazine and sulfathiazole protected only 27% and 0% respectively. Moreover, single daily doses of sulfaquinoxaline in severe pneumococcal infections compared favorably with multiple daily doses of sulfadiazine or sulfathiazole (Table I). This was found when 20 mg of sulfaquinoxaline was given as a daily dose, as compared with 20 mg of sulfadiazine or sulfathiazole divided into four 6-hourly doses of 5 mg per mouse. Both drugs protected about 50% of the mice.

Tests performed to determine the efficacy of sulfaquinoxaline when given at intervals other than every 24 hours, showed that if treatment was given every 36 or 48 hours, a dose of 40 mg/mouse of sulfaquinoxaline was not sufficient to protect mice from severe infection.

Blood Levels. The striking therapeutic effects obtained with single daily doses of sulfaquinoxaline may be explained by the fact that this drug remains in the blood for long periods of time and consequently, therapeutic blood concentrations can be maintained by infrequent drug administration. Thus, applying the method of Bratton and Marshall,[7] it was found that a concentration of 3 to 7 mg% was still present in the blood of mice 24 hours after the administration of a single dose of 20 mg per 20 g mouse. Even after 72 hours, small quantities of the drug could be detected in the blood. When the interval between treatments was extended beyond 24 hours, the blood concentration of sulfaquinoxaline fell below the effective range, with the resulting death of the animal.

Summary. Sulfaquinoxaline was found to be active against certain bacteria both *in vitro* and *in vivo*. Single daily doses of this drug were more effective than single daily doses of sulfadiazine or sulfathiazole. These findings may be explained by the fact that sulfaquinoxaline remains in the blood for long periods of time.

[7] Bratton, A. E., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

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The Demonstration of Antibodies in Lymphocytes.*

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The presence in extracts of lymphocytes of normal rabbits of a protein probably identical with the gamma globulin of normal rabbit serum[1] has led to the search for immunologically labeled globulin in lymphocytes of immunized animals. Reticulo-endothelial cells in general[2] and lymphoid tissue in par-

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[1] White, A., and Dougherty, T. F., *Abstracts of Proc. Meetings of Am. Chem. Soc.*, New York, September, 1944.

[2] Sabin, F. R., *J. Exp. Med.*, 1939, **70**, 67.